



Borderline forms of mental retardation in pre-pubertal children living in an iodine-deficient region

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ABSTRACT

Introduction: Almost a third of the world's population lives in conditions of chronic iodine deficiency, which causes the development of iodine deficiency diseases. The degree of iodine deficiency determines not only the severity of the goiter endemic, but also the increase in various disorders of somatic, mental and reproductive health. Iodine deficiency is the most common cause of mental retardation in children. This problem is especially acute for Ukraine, as almost its entire territory is considered iodine deficient. The purpose of the study is to determine the level of formation of intellectual functions of children from iodine deficiency regions. **Methods:** During 2010-2019 years, studies were conducted (questionnaires, ultrasound and hormonal examination of the thyroid gland, assessment of mental development) of 1973 children aged 7-18 during expeditions to various geographical areas of Chernivtsi region. **Results:** According to WHO criteria, Chernivtsi region meets the average (mountain zone) and mild (plain zone and Chernivtsi) degree of iodine deficiency. The concentration of iodine in the urine ranged from 17.7 µg/l to 156 µg/l. Signs of laboratory hypothyroidism were found in 11.27% of children. According to the results of the study, a decrease in the level of formation of intellectual functions (memory impairment, fine motor skills, reading speed, accuracy and productivity, instability of attention, decreased ability to concentrate) with increasing iodine deficiency. **Conclusion:** With a decrease in mental abilities in children, there is even a mild and moderate iodine deficiency, which is manifested by borderline forms of intellectual retardation. The most pronounced deviations are registered in children with subclinical hypothyroidism, which reduces their mental capacity.

Keywords: iodine deficiency, children, mental development.

1. INTRODUCTION

Territories of more than 100 countries are recognized as iodine deficient; about 30% of the world's populations live in environmentally conditioned iodine deficiency (Abel et al., 2017). According to the World Health Organization (WHO), more than 40 million people suffer from mental retardation due to iodine deficiency (Assessment, 2007). At the beginning of the 90s of the last century, International Committee for Control of Iodine Deficiency Disorders (ICCIDD) together with United Nations Children's Fund (UNICEF) and WHO had produced a national programs strategy for prevention of diseases, associated with iodine deficiency, and their control; the task was given to eliminate iodine deficiency globally around the world, including Europe (World Health Organization, 2007). The most significant social consequences of the impact of iodine deficiency on human health are borderline disorders, including intellectual retardation, which does not reach the level of intellectual disability. For Ukraine, the medical and social significance of the problem of iodine deficiency diseases (IDD) is particularly acute, as almost its entire territory is considered iodine deficient, and the end of iodine prophylaxis in the early 70s of the XX century resulted in increasing frequency and severity of iodine deficiency diseases (Horodynska et al., 2016; Pearce et al., 2013). The main problem of health care in connection with iodine deficiency is the negative impact of iodine deficiency on the intellectual potential of the population that is living in areas with environmentally caused iodine deficiency. Goiter has long been prevalent in one of the regions of Ukraine - Bukovina. The information about goiter is in the book (Fisher, 1989). Oberleutnant of the Gendarmerie Eduard Fischer, describing the sanitary conditions in which the population of Bukovina lived, pointed to frequent cases of cretinism. As for the manifestation of the disease among the Ukrainians (Ruthenians) of Bukovina, they were widespread, according to the author, in the remote communities near the river Cheremosh. Based on the high prevalence of cretinism among the inhabitants of mountainous areas, E. Fischer concluded that the disease is causally related to the geological structure of the soil. Achievements in the fight against iodine deficiency in Bukovina in the 30-70s of the last century due to the use of iodized salt, antistrumin in the 80s changed due to the end of iodine prophylaxis for recurrence of goiter endemic. In Bukovina, depending on the climatic and geographical zones, there is a mild to moderate degree of iodine deficiency.

Ukraine is the only country in Europe that does not have an iodine deficiency program. Lack of iodine in the body at the stage of formation of the brain and its functions affects the brain of the fetus and child, differentiation of tissues, especially CNS, and leads to inborn dysontogenesis of higher mental functions (Hynes et al., 2017). The WHO classifies iodine adequacy in pregnant women if the average urinary iodine concentration is 150–249 µg/l; the median urinary iodine concentration (UIC) in pregnancy <150 µg/l is considered insufficient, 250–499 µg/l, as noted above, and > 500 µg/l as excessive (Urinary Iodine, 2013). Insufficient iodine amount during gestation, especially in the first trimester, is the main cause of neurological disorders (Bath et al., 2013).

Hypothyroidism as a consequence of iodine deficiency and accompanying mental disorders in the framework of psychoendocrine syndrome occur with an extreme degree of iodine deficiency, which is almost non-existent in Ukraine (Pankiv, 2012). However, the lag in the level of intellectual development is observed in these conditions. Almost all current research is devoted to the study of IQ reduction in regions with different iodine supply. The results of the research are sometimes contradictory and ambiguous (Abel et al., 2017; Bath et al., 2013; Bath et al., 2017; Delange, 2001; Delange, 2001; Moleti et al., 2016; Zimmermann, 2006). Important questions remain unanswered: Does the mental development and formation of the psyche in the population of iodine deficiency areas in general suffer? What are the clinical consequences of such exposure? Does iodine deficiency affect the development of cognitive functions and mental health in general?

The purpose of the study is to determine the level of intellectual functions formation and the state of mental capacity of children living in a region with mild to moderate iodine deficiency.

2. METHODS

The work was performed on the basis of Chernivtsi Regional Children's Clinical Hospital during 2010-2019. We conducted research during expeditions to various geographical areas of Chernivtsi region (Putilsky, Kelmenetsky, Vyzhnytsky, Khotyn districts). A complex system of territorial units that create mountain and plain areas of residence represent the nature of the Bukovina region. These areas are selected in accordance with geographical concepts and climatic and socio-economic characteristics (Fig. 1). The examination program included: collection of anamnesis and filling in questionnaires, measurement of anthropometric indicators and assessment of intellectual development, ultrasonography of the thyroid gland, hormonometry, and the value of iodine in urine. 1973 children aged 7-18 were examined, which divided into groups according to areas of residence, age and sex. A multifaceted survey with specification of anamnesis, social, domestic, environmental, and other features of the accommodation of children was performed (eating regime, the composition of food, the use of the cafeteria, day schedule, time of doing the homework, physical activity). The questionnaire recorded data of physical and sexual development, evaluation of functioning state and the state of child's health. All children (some parents) were interviewed about use of contrast X-ray) (2 positive results were



obtained; those children were excluded from the study). For 6 months, no subjects received treatment with iodine-containing drugs and thyroid hormones.

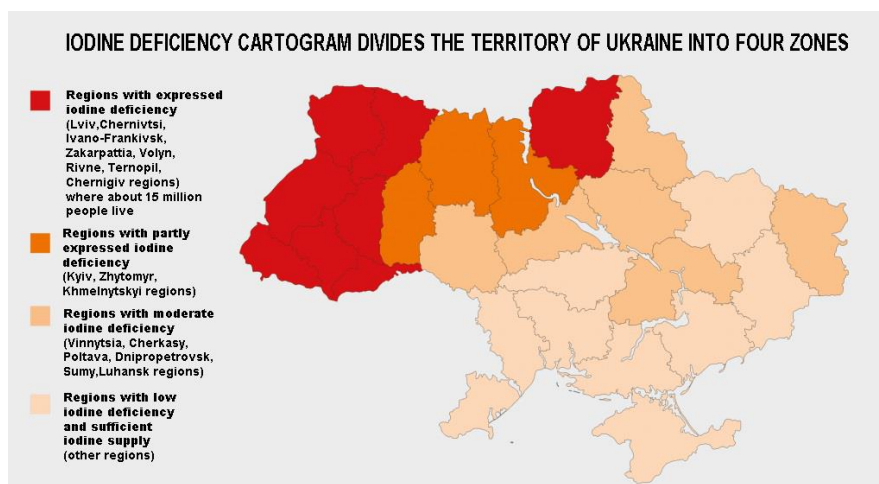


Figure 1 Division of the territory of Ukraine into zones (<https://www.vz.kiev.ua/>).

The level of formation of intellectual functions and the state of mental capacity was determined in 399 school children aged 10-16 years, including 194 boys and 205 girls. In these children were conducted clinical and laboratory studies to determine the hormonal profile. Inclusion criteria: 7-18 years; living in the Chernivtsi region, absence of research with the use of iodine-containing contrast agents; non-use of thyroid hormones and iodine-containing drugs in the last 6 months; absence of somatic pathology of the central nervous system. Exclusion criteria from the study: change of territory of residence, research with the use of iodine-containing contrast agents; use of thyroid hormones and iodine-containing drugs.

Assessment of the morphofunctional state of the thyroid gland (TG) was performed according to the indicators of visual-manual examination. According to the WHO classification, the degree of the TG is palpable, the particle size corresponds to the distal phalanges of the patient - I degree, the particle size exceeds the size of the patient's distal phalanges - II degree; the particle size exceeds the size of the distal phalanges - III. Ultrasonographic examination of the TG was performed on a Scanner - 100 using a linear sensor with a frequency of 7.5 mHz.

According to the parameters obtained during the ultrasonography, the volume of each thyroid lobe was calculated according to the formula: maximum thickness /cm/ x width /cm/ x length /cm/ x 0.478 and compared with the recommended thyroid volumes obtained during the examination of children in iodine-supplied regions Europe, taking into account age, sex and body area (WHO classification of goiter, 2001; Zimmermann et al., 2004). The functional state of the pituitary-thyroid system was assessed by clinical symptoms using screening integrated tables, as well as standard kits for RIA T_3 - "RIO- T_3 -PG", T_4 - "RIO- T_4 -PG", (Belarus), standard test kits from Mallinckrodt (Germany) minus the TSH/ T_4 index determined the concentration of thyroid - stimulating hormone (TSH).

Blood sampling for hormonal examination was from the ulnar vein. Sample counting and processing of results were performed using an automatic counter with a microprocessor and computer data processing. Taking into account that the concentration of iodine in a single portion of urine correlates well with the level of iodine in daily urine, we took urine from children in test tubes by 5 ml of urine at a time. The concentration of iodine was determined by cerium-arsenite method with preliminary wet ashing of its samples. According to the obtained data, the median ioduria was calculated, which was expressed in μg of iodine per 1 liter of urine. The level of intellectual functions formation of children was carried out after acquaintance with the state of their health, exclusion of mental disorders and neurological pathology, assessment of the state of auditory and visual analyzers. A fragment of R. Kettel's test was used (Adapted modified version of R. Kettel's children's personality questionnaire) (Aleksandrovskaya et al., 1985). The methodology was constructed of 10 questions, where the correct answer was evaluated in one point. The sum of points was translated into standard grades - "sthenes" which determined the low (1-3 sthenes), medium (4-7) and high (8-10) level of intelligence.

Determination of indicators of mental activity of school-age children, assessment of the pace of psychomotor activity and the ability to perform monotonous work that requires concentration, was performed using a proofreading test in combination with check of reading speed (Perelesni, 1980). To determine the speed of reading, a text was proposed, which was selected according to age, and contained from 140 to 400 words. The text was printed on separate sheets and distributed to a certain group of children (6-

8 people) so that to control the quality of the task. The number of silent words read in one minute determined reading speed. For proofreading, special age-appropriate forms were used, where a number of words were printed, among which the letter combination "an" was emphasized in one minute.

The characteristic of attention was determined using the indicator of accuracy of work (W), which characterizes the quality of the task. If no error or omission is made, this value is 1.0. Otherwise, $W < 1.0$. $W = \Sigma / \Sigma + O$ (Σ - the number of correctly underlined characters, O - the number of missed and incorrectly marked characters. Indicator of stability of attention (productivity) (E) - determines both the quality and pace of execution, taking into account the amount of material done. If $W = 1.0$ (no errors), this figure is expressed as an integer. When $W < 1.0$, E is a small number. $E = S \times W$, where W is the accuracy of the work, S is the number of words that the child had time to look through.

The obtained results were processed by the method of statistical variation and correlation analysis. Statistical processing included the calculation of the arithmetic mean of each of the indicators (M), the standard deviation (σ). Evaluation of the probability of the results involved determining the mean error of the arithmetic mean (m), the probability of differences in the mean values by t - Student's criteria. The computer program "Biostat" was used for statistical processing.

The study follows ethical principles for people who act as subjects of research, taking into account the main provisions of the GCR ICH and the Helsinki Declaration of the World Medical Association for Biomedical Research, where the person acts as their object (World Medical Association Declaration of Helsinki 1964, 2000, 2008), Council of Europe Convention on Human Rights and Biomedicine (2007) on the positive conclusion of the Commission on Bioethics of the Bukovinian State Medical University (protocol No. 5; 16.04.2017) and the local commission on biomedical ethics at the «Chernivtsi Regional Children's Clinical Hospital» (protocol No.9; 18.05.2017). This included adherence to the informed consent concept, consideration of the benefits over harm of risk, the principle of confidentiality and respect for the child's personality as a non-self-protective person, and other ethical principles for the children under study.

3. RESULTS

The children were divided into subgroups by age, sex and area of residence (Tables 1 and 2).

Table 1 Distribution of children by age and area of residence

Area of residence	Age of children (years)												Total
	7	8	9	10	11	12	13	14	15	16	17	18	
Chernivtsi	43	40	40	40	50	44	47	46	60	80	25	28	543
Mountain area	80	81	73	81	86	87	65	59	65	89	53	50	869
Plain area	29	39	45	45	60	60	48	61	58	60	27	29	561
Total	152	160	158	166	196	191	160	166	183	229	105	107	1973

Table 2 Distribution of surveyed children by sex and area of residence

Area of residence	Boys	Girls	Total
Chernivtsi	258	285	543
Mountain area	405	464	869
Plain area	264	297	561
Total	949	1024	1973

Most of the children we examined were lived in satisfactory social and living conditions. 7.09% of respondents indicated unfavorable living conditions. For material support 12.67% of families believe that they live well, 25.34% have good material support, 46.62% - satisfactory, 15.37% - poor. 91.23% of children live in complete families. Most of their parents had secondary education (65.88%). 5.57% had incomplete secondary education, 28.55% - had higher education. Mothers have distributed as follows: higher education - 27.62%, secondary - 66.90%, lower secondary - 5.48%. 45.10% of parents and 76.44% of mothers do not drink alcohol. Occasionally drink 47.39% of parents and 22.80% of mothers. 7.51% of surveyed parents and 0.76% of mothers drink alcohol systematically. 50.90% of parents do not smoke, 33.19% smoke up to 20 cigarettes and 15.91% - more than 20 cigarettes per day. 5.48% of mothers smoke regularly. 91.23% of mothers do not smoke and 3.29% of mothers occasionally smoke.

The menu of the respondents was dominated by bread and flour products (66.90%), dairy products consumed only 55.2%, meat - 33.19%, vegetables - 47.39%, fish products – 5.48%. It should be noted that according to the results of the study, no child from the surveyed group consumes seafood rich in iodine, iodized salt is used only by 1 family out of 50, but they also use and store salt without basic hygiene requirements. The diet of most children consists of local products, including those grown in backyards, which in conditions of natural iodine deficiency contain little iodine. Children showed a number of complaints: rapid fatigue (11.9%), decreased memory (5.48%), poor sleep (3.25%), periodic headache (33.1%), abdominal pain (22.80%), heart area (27.62%), pain of other localization - 7.63%.

The results of determination of iodine in the urine of 399 children were characterized by a high amplitude of fluctuations (17.7 $\mu\text{g/l}$ - 156 $\mu\text{g/l}$) with average values of 55-70 $\mu\text{g/l}$. Analysis of the distribution of iodine concentration in the urine of children living in areas with different levels of iodine deficiency is presented in table 3.

Table 3 Indicators of iodine concentration distribution in children's urine

Area of residence	Coefficient of asymmetry	Coefficient of eccentricity	Probability of coincidence of actual distribution with normal (by criterion χ^2)
Chernivtsi	4,56	26,58	$4,5 \times 10^{-7}$
Mountain area	1,03	3,67	$3,6 \times 10^{-8}$
Plain area	1,33	4,87	$3,5 \times 10^{-4}$

The median of ioduria in children from the plains and Chernivtsi was $67.54 \pm 4.02 \mu\text{g/l}$ and $69.32 \pm 3.99 \mu\text{g/l}$ which corresponds to the WHO criterion of mild iodine deficiency; and in children from mountainous areas - $29.34 \pm 3.11 \mu\text{g/l}$ corresponds to the average degree of iodine deficiency. The results of the study showed that children for the most part have an average degree of intellectual development (240, 60.15%) (Figure 2). As the degree of iodine deficiency increased, the level of intellectual formation changed downward.

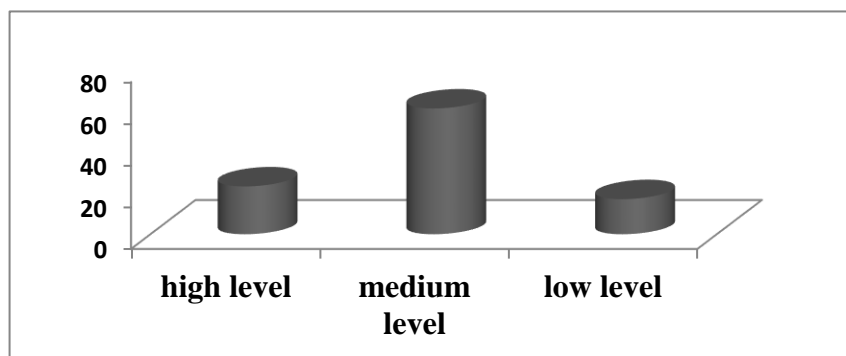


Figure 2 Distribution of surveyed children according to the level of formation of intellectual functions (%).

Changes in most of the studied cognitive functions were found in 50 (12.53%) children from the zone of iodine deficiency. The frequency of cognitive impairment depending on the area of residence is presented in Fig.3.

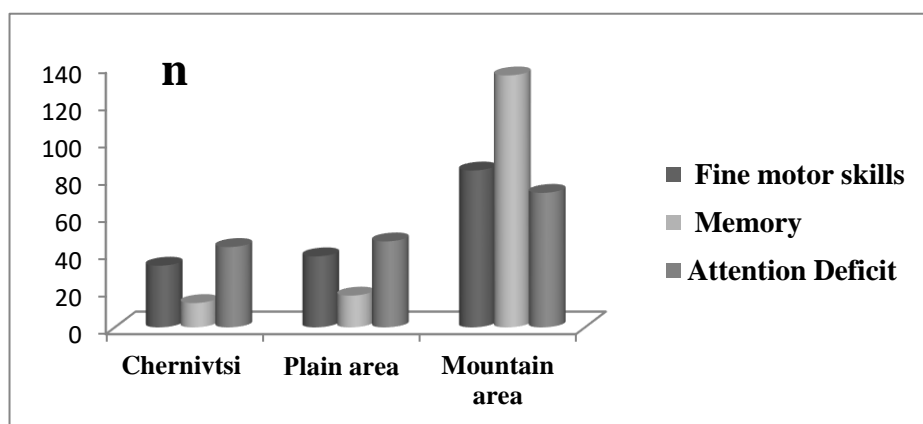


Figure 3 Number of children with cognitive impairment from different areas of residence.

Thyroid dysfunction (signs of laboratory hypothyroidism) was found in 45 of 399 examined children (11.27%). Among children with laboratory hypothyroidism, the number of those who had a low level of intelligence was 2.7 times higher than among children without thyroid dysfunction (33.3 vs. 12.42%, $p < 0.01$, Fig.4).

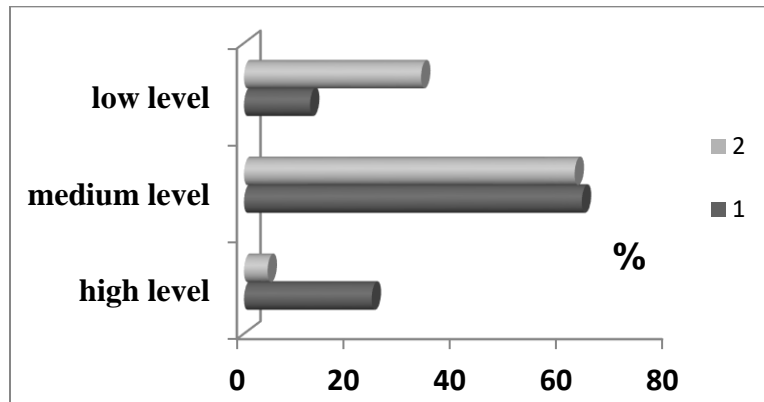


Figure 4 Frequency of cognitive impairment in children depending on the functional state of the thyroid gland.

Note: 1 - group of children with laboratory hypothyroidism; 2 - a group of children without thyroid dysfunction

The leading deviations in the whole group of children were impairments of memory and fine motor skills (68.7%). The structure of cognitive deficiency in children is presented in Fig.5.

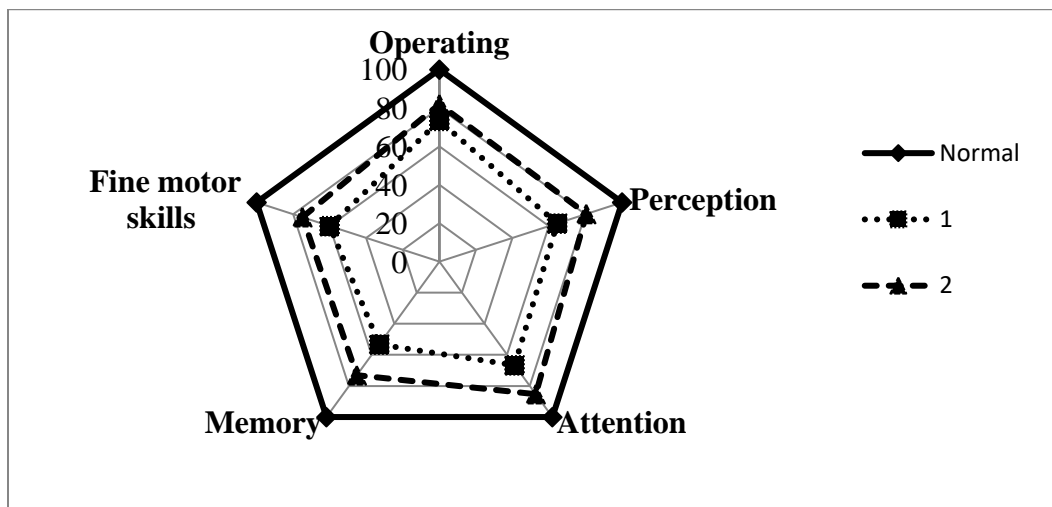


Figure 5 Frequency of disorders of cognitive function in children (%).

Note: 1 - group of children with laboratory hypothyroidism; 2 - a group of children without thyroid dysfunction. Indicators of cognitive functions of children in the comparison group (living under conditions of sufficient iodine supply) are taken as 100%.

It is established that slightly lower indicators of basic cognitive functions characterize children from iodine-deficient living area. Correlative analysis revealed a positive highly-likely positive connection of medium strength in children about pre-puberty age between the TG volume and rates of fine motor skills ($r = 0.541$, $P < 0.01$), memory ($r = 0.491$, $P < 0.05$) and efficiency ($r = 0.455$, $P < 0.05$). 199 prepubertal children were selected to determine the rate of reading speed, accuracy and productivity of the work. We observed a difference in terms of speed reading of children depending on the level of iodine deficiency: in boys the indicator is equal to 162.12 ± 9.11 (area with mild iodine deficiency) and 132.23 ± 9.47 (with moderate iodine deficiency, $P < 0.05$) in girls, respectively, 181.33 ± 10.87 and 151.65 ± 8.17 ($P < 0.05$). The reading speed increases with age both in the group of children from the zone with normal iodine supply and in the group of children from the zone of iodine deficiency. However, in children from the iodine deficiency zone, the rate of increase in reading speed is slow ($P > 0.05$). This is especially true for children with subclinical hypothyroidism (reading speed 134.23 ± 9.27 ; $P < 0.01$). The results of the proofreading test are shown in table 4.

Table 4 Indicators E and W in school-age children depending on gender and area of residence

Indicators	Plain area (n= 93)				Mountain area (n=106)			
	Boys		Girls		Boys		Girls	
	n	M ± m	n	M ± m	n	M ± m	n	M ± m
E	46	34,99± 2,19	47	32,21 ± 2,22	52	23,88 ± 2,43**	54	27,31 ± 2,15
W		0,69 ± 0,04		0,66 ± 0,06		0,61 ± 0,02*		0,54 ± 0,04*

Note. * - $P < 0.05$; ** - $P < 0.01$ relative to the indicators in children of the plain zone

Comparison of the coefficient of accuracy and productivity in children of the plains and mountains allows us to conclude that children living with moderate iodine deficiency have deterioration in productivity and a decrease in its accuracy. Regarding the indicators of the accuracy of the work, a probable difference ($P < 0.05$) occurs when comparing boys and girls in total, as well as boys of puberty ($P < 0.001$). At the same time, work productivity in girls tended to decrease, and in boys it was authentically lower ($P < 0.01$). Authentically lower productivity in total (boys and girls) living with iodine deficiency of moderate severity ($P < 0.05$).

4. DISCUSSION

The daily intake of iodine with food, recommended by the WHO, the UNICEF and the ICCIDD, is 90 mcg for preschool children (0 to 59 months), 120 mcg for schoolchildren (6 to 12 years), 150 mcg for adolescents (over 12 years) and adults, 250 mcg for pregnant and lactating women (World Health Organization, 2007). Failure to comply with these requirements is responsible for a number of adverse health effects known as IDD (Iodine Global Network, 2016). They affect almost 1.9 billion people worldwide and are a major health issue in various countries, including Ukraine (Hay et al., 2019; Iodine Global Network, 2017; Pankiv, 2016; Lazarus, 2014; Hynes et al., 2013; Urinary Iodine Concentrations, 2013). Particularly relevant are the detrimental effects of insufficient iodine intake by the mother on the development and maturation of the fetal brain. It is known that nocturnal disorders of intellectual development occur in severe iodine deficiency in mother during pregnancy, including the development of cretinism (Zimmermann, 2012). Correction of severe iodine deficiency in the population reduces cretinism (Zimmermann, 2011) and increases the level of IQ of the offspring (Sun et al., 2017). Insufficient iodine during gestation, especially in the first trimester, is the main cause of neurological and mental disorders in offspring (Pankiv, 2016). Consequences of severe iodine deficiency are well established. Today, there is growing evidence that even mild iodine deficiency can have a small but noticeable effect on offspring. Studies (Pearce et al., 2013) have highlighted the effects of mild gestational iodine deficiency (GID): decreased IQ, including verbal IQ, reading accuracy, and reading comprehension. Studies (Abel et al., 2017; Moleti et al., 2016) confirm these findings. Talyor et al., (2014), reported that IQ levels were lower in offspring (aged 3 years) of mothers with impaired thyroid function.

The effect of mild to moderate iodine deficiency on mental development is less well-known than the effect of severe iodine deficiency, but it is important because moderate iodine deficiency predominates in many countries, including Ukraine (Baldini et al., 2019; National Center for Health Statistics, 2018; Pankiv, 2017; American Thyroid Association, 2017). A number of studies conducted in pregnant women with mild to moderate iodine deficiency indicate cognitive impairment in children (Leite et al., 2017; Alexander et al., 2017; Zimmermann et al., 2015). Our study demonstrates certain associations between living in an iodine deficiency zone and borderline intellectual disabilities that persist until adolescence, despite the fact that children attend public education establishments.

Given that the median ioduria indicates iodine intake over the past 24 hours and may not reflect the individual iodine level of a particular child. However, this suggests that in some periods of development, even short, when the body did not receive enough iodine. The results (Pearce et al., 2013) indicate that memory and the speed of auditory processing are affected by insufficient iodine supply in utero. However, the development of the brain does not stop in utero, and for constant optimal neurodevelopment requires nutrition with sufficient use of iodine-containing foods during childhood. We recognize that the median ioduria is not an ideal indicator of a person's current or long-term iodine status. The last level of iodine in childhood is likely to have a positive effect on cognitive development, as evidenced by indicators of intellectual development of children in the area of living with a good supply of iodine. Due to persistently low readings, accuracy, and productivity, even a sufficient amount of iodine in childhood may not correct all deficiencies caused by iodine deficiency in utero or early childhood. We agree that adequate maternal iodine supply in early pregnancy is crucial for fetal neurodevelopment (Vitamin and Mineral Nutrition Information System, 2013), and there is growing evidence that adequate maternal thyroid stores before pregnancy are also important (Abel et al., 2017). However, the results support the notion that lack of working memory and processing speed are potential drivers of literacy for those affected by moderate gestational iodine deficiency. Despite the mandatory enrichment and recommendations for daily iodine supplementation during

pregnancy, some expectant mothers still appear to have a mild iodine deficiency during pregnancy. Further research will be needed to confirm these preliminary observations.

Our findings confirm previous studies that indicate that even moderate and iodine deficiency may affect cognitive performance in children. We have shown that a decrease in mental abilities in children is observed even with mild and moderate iodine deficiency. In children with a high and medium level of intellectual development, sufficiently developed abstract forms of thinking, a large amount of knowledge were observed. Children with a low level of intelligence were dominated by a primitive approach to solving logical problems; they were dominated by specific forms of thinking. In terms of reading speed in the examined children, we obtained a probable difference depending on living in areas with varying degrees of iodine deficiency. The best improvement of children's mental capacity in the learning process was registered under conditions of higher iodine supply.

One of the criteria for students to adapt workload and an important indicator of health is mental efficiency. Mental performance is characterized by the speed of information processing, quality and productivity of mental work, the severity of the force of arousal. Thus, our studies revealed some changes in the cognitive performance of children with laboratory hypothyroidism. It can be predicted that in order to achieve high or medium success in school, all the compensatory capabilities of the body are involved, which, of course, can be a risk factor for the development of psycho-emotional and somatic disorders. Action is needed to address this preventative condition and ensure that more children are able to reach their full cognitive potential.

5. CONCLUSION

Children from the iodine deficiency zone have borderline forms of intellectual retardation. The leading deviations in the whole group of children were impairments of memory and fine motor skills. The level of intellectual formation, productivity and accuracy of work changed in the direction of decreasing with increasing degree of iodine deficiency. Among children with subclinical hypothyroidism, the number of those who had a low level of intelligence was twice as high, they have instability of attention, decreased ability to concentrate, reduced productivity, which generally reduces their mental capacity.

Competing interests

The authors declare that they have no competing interest

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Authors' contribution

All authors shared in this study design; they reviewed literature, and wrote the primary draft of the manuscript. All authors read and approved the final manuscript.

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Abbreviations

TG -	thyroid gland
UNICEF -	United Nations Children's Fund
WHO -	World Health Organization
ICCIDD -	International Committee for Control of Iodine Deficiency Disorders
IDD -	Iodine deficiency diseases
UIC -	urinary iodine concentration
TSH -	thyroid - stimulating hormone
W -	Accuracy of work
E -	Productivity

Data and materials availability

All data associated with this study are present in the paper.



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